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Case Report

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Thromboembolic complication of nephrotic syndrome: a case of pulmonary embolism

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ABSTRACT

Pulmonary thromboembolism (PTE) is a common, potentially fatal condition that can be challenging to diagnose. While risk factors like lower extremity fractures, myocardial infarction, immobilization, and malignancy are well known, nephrotic syndrome is a rare secondary cause. We present a 28-year-old male hospitalized with suspected nephrotic syndrome. On the second day of admission, he developed sudden chest pain and shortness of breath. Although he was hemodynamically stable, chest X-ray showed increased opacity in the right lower lung zone, suggesting infarction. Elevated D-dimer levels and right heart enlargement on bedside echocardiography raised suspicion of PTE, and anticoagulant treatment was initiated. CT pulmonary angiography confirmed thrombi in the right pulmonary artery and infarct areas. This case illustrates the rare coexistence of nephrotic syndrome and acute PTE in a young adult and underscores the importance of recognizing radiological signs and considering prophylactic anticoagulation.

Keywords: Nephrotic syndrome, membranous nephropathy, pulmonary thromboembolism, venous thromboembolism, young adult

INTRODUCTION

Venous thromboembolism (VTE) includes pulmonary thromboembolism (PTE) and deep vein thrombosis (DVT).[1]

VTE is more common in older adults. Studies show a mean age above 50, with over half of cases occurring after age 65.[2]

PTE has high mortality and morbidity. Early diagnosis is essential and depends on clinical signs and identification of risk factors. These include genetic (primary) and acquired (secondary) causes. Nephrotic syndrome is a less frequent secondary cause.[2]

Patients with nephrotic syndrome have a well-known tendency for thromboembolic events. These events can involve both veins and arteries. PTE occurs in 1% to 20% of cases, with membranous nephropathy being particularly high-risk.[3]

There are no prevalence studies showing how often nephrotic syndrome appears in patients with PTE. The coexistence of both conditions is rare and needs further study.

This report presents a young adult who developed PTE while hospitalized for nephrotic syndrome.

CASE

A 28-year-old male with no known comorbidities or medication history presented to the internal medicine outpatient clinic with complaints of fatigue and bilateral leg swelling. Laboratory results revealed serum albumin of 18.9 g/L, urine protein 3+, and a spot urine protein/creatinine ratio of 20.573 mg/g. The patient was hospitalized by the nephrology department with a preliminary diagnosis of nephrotic syndrome. Further evaluation showed 6.613 mg/day of albumin and 8.432 mg/day of total protein in 24-hour urine collection. A renal biopsy was planned to investigate the underlying etiology. On the second day of hospitalization, the patient experienced sudden onset dyspnea, chest pain, and sharp back pain.

Postero-anterior chest radiograph taken in hospital application is provided in **Figure 1a**. Additionally, **Figure 1b** presents the anteroposterior chest radiograph of the patient, demonstrating the area of infarction (a pleural-based, irregular opacity in the right lower lung zone).

D-dimer was elevated at 2.4 µg/mL, while troponin levels were within normal limits, and ECG showed no ischemic changes. Arterial blood gas was pH 7.39, pCO_2 40 mmHg, HCO_3 24

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Figure 1a. Postero-anterior chest radiograph taken in hospital application

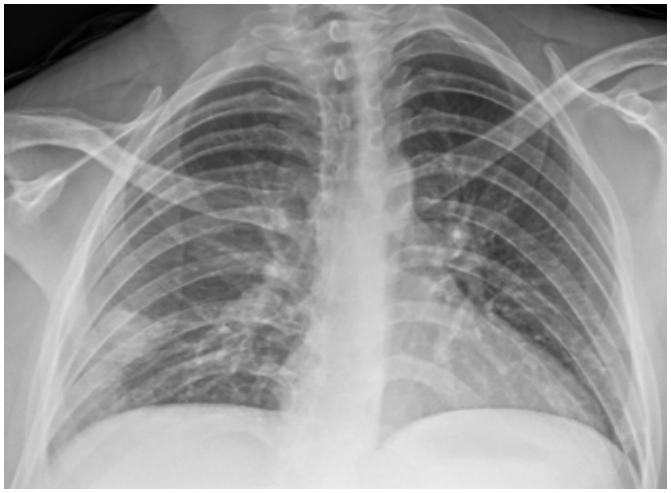

Figure 1b. Antero-posterior chest radiograph withdrawn when complaints started

Figure 2a. Intraluminal thrombus in right main pulmonary artery middle lobe

Figure 2b. Intraluminal thrombus in right main pulmonary artery lower lobe

mmol/L, and lactate 1.1 mmol/L. Acute phase reactants were unremarkable. Echocardiography showed an ejection fraction (EF) of 60%, systolic pulmonary artery pressure (sPAP) of 35 mmHg, and mild right chamber dilation. No thrombus was detected on bilateral lower extremity doppler ultrasound. The pulmonary embolism severity index (PESI) score was 1, and sPESI was 0, classifying the patient as low-risk PTE based on early mortality criteria. Anticoagulation was initiated with enoxaparin 0.6 ml twice daily, considering renal function and bleeding risk. CT pulmonary angiography (CTPA) performed 48 hours later revealed filling defects in the distal right main pulmonary artery extending to segmental branches of the middle and lower lobes (**Figure 2a, 2b**). Additionally, peripheral ground-glass consolidation with lobulated margins at the right lower lobe's basal segments suggested infarction (**Figure 3**).

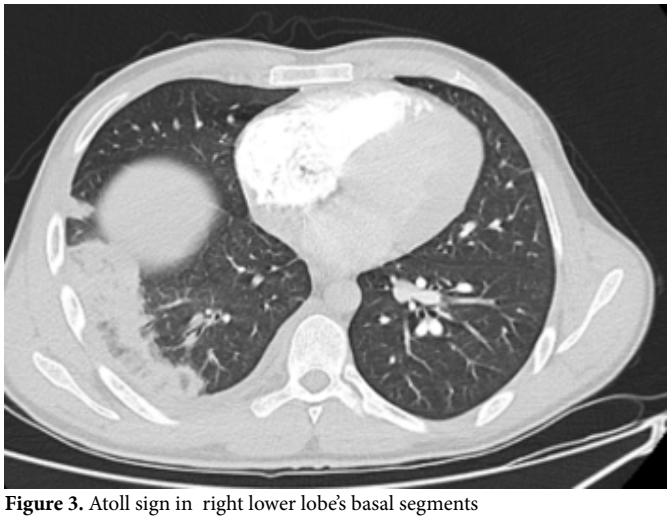

Figure 3. Atoll sign in right lower lobe's basal segments

This finding is known as the "reverse halo" or "atoll sign," a radiologic marker occasionally associated with PTE. Enoxaparin sodium and warfarin were administered concomitantly for 5 days. Once the INR reached the therapeutic range (2.0–3.0), enoxaparin was discontinued, and warfarin was continued. The warfarin dose was adjusted to maintain the INR within this range. The patient was planned to receive warfarin therapy for at least 6 months and is currently still on warfarin treatment. The patient will be followed up at regular intervals, and future decisions regarding anticoagulation will be based on clinical status and imaging to assess the risk of PTE.

Due to the patient's young age, thrombophilia screening was performed, revealing heterozygous mutations in factor V Leiden and factor C, and a homozygous mutation in MTHFR; no mutations were detected in protein C, protein S, or antithrombin III.

Based on hematology recommendations, anticoagulation was planned for a minimum of six months. The renal biopsy

was postponed, and anti-PLA2R antibodies were detected, confirming a diagnosis of membranous glomerulonephritis. In the treatment of membranous glomerulonephritis, the patient received 1.000 mg of intravenous rituximab on days 1 and 15. Pre-treatment infection screening was conducted, and premedication was administered to prevent infusion-related reactions. Clinical response was monitored via proteinuria and serum albumin levels. The treatment was well tolerated. In case of relapse during follow-up, additional dosing was planned.

DISCUSSION

Nephrotic syndrome is a hallmark of glomerular disease characterized by increased glomerular permeability to macromolecules, especially albumin, resulting in nephrotic-range proteinuria (>3.5 g/day). The classic clinical manifestations include hypoalbuminemia, hyperlipidemia, edema, and a hypercoagulable state. These features significantly contribute to the morbidity and mortality associated with nephrotic syndrome. Thromboembolic risk is a well-documented complication in nephrotic syndrome. The incidence of venous thrombosis has been reported around 15%, pulmonary embolism between 10–30%, and renal vein thrombosis in 25–37% of cases.[4,5] The hypercoagulable state is attributed to multiple mechanisms including increased hepatic synthesis of procoagulants (e.g., fibrinogen, factor V, factor VIII), heightened platelet activity and aggregation, reduced fibrinolytic activity, local activation of coagulation within the kidney, and urinary losses of natural anticoagulants such as antithrombin III.

However, the role of prophylactic anticoagulation in patients with nephrotic syndrome remains controversial.[6] In a retrospective study evaluating 298 patients with primary and secondary nephrotic syndrome, the risk of thromboembolism was found to be eight times higher than the general population over a 10-year period. The highest risk was observed within the first six months and was strongly associated with the degree of proteinuria and hypoalbuminemia.[6] A 2023 study published in Medicina Clinica explored the predictive value of phospholipase A2 receptor (PLA2R) antibodies in membranous nephropathy. Anti-PLA2R positivity, a marker of disease activity in primary membranous nephropathy, was associated with a significantly higher risk of VTE compared to anti-PLA2R negative cases.[7] According to the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, anticoagulation should be considered in membranous nephropathy patients with serum albumin levels below 2.0–2.5 g/dl and additional risk factors, albeit with a low level of evidence (2C). The guideline recommends full-dose anticoagulation in nephrotic syndrome patients who develop a thromboembolic event.[7] Limited data exists on outcomes of patients receiving prophylactic anticoagulation. The only controlled study on this topic was a retrospective analysis by Kelddal et al.[9], suggesting a cautious use of anticoagulation—especially in patients with serum albumin <2 g/dl—in combination with aspirin may be beneficial. Similarly, a 2024 meta-analysis by de Pascalini[8] reported that, although associated with a non-negligible risk of bleeding, prophylactic anticoagulation significantly reduces the risk of VTE in adult patients with primary nephrotic syndrome. In this case, the patient presented with nephrotic syndrome and respiratory symptoms suggestive of thrombosis. The diagnosis of PTE was supported by imaging findings showing thrombi in the pulmonary arteries and the presence of a “reverse halo” sign in the lung parenchyma. The patient responded well to anticoagulation therapy, initially with enoxaparin and subsequently with warfarin. This case highlights the importance of considering PTE in young patients with nephrotic syndrome who develop respiratory complaints and raises the issue of whether prophylactic anticoagulation should be routinely considered in such high-risk individuals.

CONCLUSION

Nephrotic syndrome is a significant risk factor for VTE. Patients should be systematically evaluated for thromboembolic complications. In young individuals with nephrotic syndrome presenting with chest pain and dyspnea, the possibility of pulmonary embolism must be promptly considered and investigated.

ETHICAL DECLARATIONS

Informed Consent
The patient signed and free and informed consent form.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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